



Abdominal adiposity and cardiometabolic risk factors in children and adolescents

A Mendelian randomization analysis

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1 **Abdominal adiposity and cardiometabolic risk factors in children and adolescents; a Mendelian**
2 **randomization analysis**

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109 **Short running head:** Abdominal adiposity and metabolic risk in children

110 **Abbreviations:** GRS= genetic risk score; WHR= waist-hip ratio; WHR_{adjBMI} = waist-hip ratio
111 adjusted BMI

112

113

114 **Abstract**

115 **Background:** Mendelian randomization studies in adults suggest that abdominal adiposity is causally
116 associated with increased risk of type 2 diabetes and coronary heart disease in adults, but its causal
117 effect on cardiometabolic risk in children remains unclear.

118 **Objective:** To study the causal relationship of abdominal adiposity with cardiometabolic risk factors
119 in children by applying Mendelian randomization.

120 **Design:** We constructed a genetic risk score using variants previously associated with waist-hip ratio
121 adjusted for BMI ($\text{WHR}_{\text{adjBMI}}$) and examined its associations with cardiometabolic factors by linear
122 regression and Mendelian Randomization in a meta-analysis of six cohorts, including 9,895 European
123 children and adolescents aged 3-17 years.

124 **Results:** $\text{WHR}_{\text{adjBMI}}$ genetic risk score was associated with higher $\text{WHR}_{\text{adjBMI}}$ (beta=0.021 SD/allele,
125 CI95% 0.016, 0.026, $P=3\times 10^{-15}$) and with unfavorable concentrations of blood lipids (higher LDL
126 cholesterol: beta=0.006 SD/allele, 95% 0.001, 0.011, $P=0.025$; lower HDL cholesterol: beta=-0.007
127 SD/allele, CI95% -0.012, -0.002, $P=0.009$; higher triglycerides: beta=0.007 SD/allele, CI95% 0.002,
128 0.012, $P=0.006$). No differences were detected between pre-pubertal and pubertal/post-pubertal
129 children. The $\text{WHR}_{\text{adjBMI}}$ genetic risk score had a stronger association with fasting insulin in children
130 and adolescents with overweight/obesity (beta=0.016 SD/allele, CI95% 0.001, 0.032, $P=0.037$) than
131 in those with normal weight (beta=-0.002 SD/allele, CI95% -0.010, 0.006, $P=0.605$) (P for
132 difference=0.034). In a two-stage least-squares regression analysis, each genetically instrumented one
133 SD increase in $\text{WHR}_{\text{adjBMI}}$ increased circulating triglycerides by 0.17 mmol/l (0.35 SD, $P=0.040$),
134 suggesting that the relationship between abdominal adiposity and circulating triglycerides may be
135 causal.

136 **Conclusions:** Abdominal adiposity may have a causal, unfavorable effect on plasma triglycerides
137 and potentially other cardiometabolic risk factors starting in childhood. The results highlight the
138 importance of early weight management through healthy dietary habits and physically active
139 lifestyle among children with tendency for abdominal adiposity.

140 **Introduction**

141 Childhood obesity has increased worldwide during the last four decades (1) and is associated with
142 cardiometabolic impairments, including insulin resistance, dyslipidemia, and hypertension in young
143 age (2). Obesity during childhood often tracks into adulthood where it is associated with an increased
144 risk and earlier onset of type 2 diabetes and cardiovascular disease (3). It is crucial to fully understand
145 the factors that contribute to increased cardiometabolic risk starting in childhood, in order to develop
146 early interventions and treatment strategies to risk groups.

147 Observational studies in adults suggest that obesity is a heterogeneous condition and
148 that for any given amount of body fat, its regional distribution, particularly when located within the
149 abdominal cavity, is an independent risk factor of cardiometabolic disease (4). In this regard, waist
150 circumference has been shown to add to BMI in risk assessment. A study implementing a Mendelian
151 randomization approach suggested that the link between abdominal adiposity and cardiometabolic
152 risk may be causal (5). Mendelian randomization utilizes the random assortment of genetic variants
153 at conception to reduce and limit confounding and reverse causality (6). When using a genetic risk
154 score (GRS) comprising 48 known variants for waist-hip ratio (WHR) adjusted for BMI (WHR_{adjBMI})
155 (7), a genetically instrumented increase in WHR_{adjBMI} was associated with higher levels of
156 triglycerides, 2-hour glucose, and systolic blood pressure, as well as an increased risk of type 2
157 diabetes and coronary heart disease, suggesting that the relationship between abdominal adiposity
158 and cardiometabolic risk may be causal in adults (5). Similar to adults, increased WHR indicates
159 abdominal adiposity in childhood (8), and gene variants increasing WHR_{adjBMI} have been associated
160 with a higher ratio of visceral to subcutaneous fat in children and adolescents (9). However, it remains
161 unclear whether abdominal adiposity is causally linked to increased levels of blood lipids, insulin
162 resistance, and blood pressure among children and adolescents (10-13).

163 In the present study, we aimed to examine the causal relationships of abdominal
164 adiposity with cardiometabolic risk factors by applying Mendelian randomization in a meta-analysis
165 of 9,895 children and adolescents from the United Kingdom, Finland, and Denmark.

166

167 **Methods**

168 *Study populations*

169 The present study includes i) 5,474 children 8-11 years of age from the Avon Longitudinal Study of
170 Parents and Children (ALSPAC) (14, 15); ii) 2,099 Finnish children and adolescents 3-18 years of
171 age from the Cardiovascular risk in Young Finns Study (YFS) (16); iii) 705 Danish children and
172 adolescents 3-18 years of age with overweight or obesity as well as a population-based control sample
173 consisting of 361 Danish children and adolescents 6-17 years of age from The Danish Childhood
174 Obesity Biobank (17); hereafter named TDCOB cases and controls, respectively; iv) 470 Finnish
175 adolescents 14-15 years of age from the Special Turku Coronary Risk Factor Intervention Project
176 (STRIP) (18); v) 460 Finnish children 6-9 years of age from the Physical Activity and Nutrition in
177 Children (PANIC) study (19) and vi) 326 Danish children 3 years of age from the Småbørns Kost Og
178 Trivsel (SKOT) I and II studies (20). (**Supplemental Figure 1**). Details on the recruitment, inclusion
179 criteria and ethical approvals of the participating studies are presented in **Supplemental Methods**.

180 Children with a history of type 1 or type 2 diabetes, mental or developmental disorders,
181 or monogenic obesity; children with medication for hypercholesterolemia or hypertension; children
182 of non-European genetic ancestry based on genome-wide principal component analysis (YFS,
183 TDCOB, STRIP and SKOT) or self-reported ethnicity (ALSPAC, PANIC), were excluded. For twin-
184 pairs, one twin was excluded. The categories of self-reported ethnicity in the ALSPAC cohort were
185 “black”, “yellow”, and “white”. The categories of self-reported ethnicity in the PANIC cohort were
186 “Caucasian” and “non-Caucasian”. We excluded all ALSPAC participants whose self-reported
187 ethnicity was “black” or “yellow”, and PANIC participants whose self-reported ethnicity was “non-

188 Caucasian”, due to these ethnicities being considered to represent non-European genetic ancestry for
189 whom the genetic architecture (allele frequencies, effect sizes) differ from European genetic ancestry.
190 The analytic codes for the exclusion of participants in the ALSPAC and PANIC cohorts based on
191 self-reported ethnicity are provided in the **Supplemental Methods**.

192

193 *Measurements of body size and composition, cardiometabolic risk factors, and pubertal status*

194 Body height and body weight were measured in all studies, and BMI was calculated as body weight
195 (kg) divided by height squared (m^2). BMI-SDS was calculated according to UK (ALSPAC) (21),
196 Finnish (PANIC, STRIP and YFS) (22) and Danish (SKOT, TDCOB cases and TDCOB controls)
197 (23) national reference values. Waist circumference was measured at mid-distance between the
198 bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of
199 the greater trochanters. Body fat mass, body lean mass, and body fat percentage were measured using
200 bioimpedance analysis (STRIP, SKOT) or dual-energy X-ray absorptiometry (PANIC, ALSPAC,
201 TDCOB). Blood pressure was measured manually using calibrated sphygmomanometers (PANIC,
202 YFS) or an oscillometric device (ALSPAC, TDCOB, STRIP, SKOT). Blood samples were taken after
203 an overnight fast in ALSPAC, YFS, TDCOB, STRIP and PANIC studies and after >2h fasting in
204 SKOT. Plasma glucose was measured using the hexokinase method, and serum insulin was analyzed
205 by immunoassays. Triglycerides, total, LDL, and HDL cholesterol were measured enzymatically.
206 Overweight and obesity were defined using the age- and sex-specific BMI cut-offs of the International
207 Obesity Task Force (IOTF) (24). In YFS, TDCOB cases, STRIP, and PANIC studies, the research
208 physician or the study nurse assessed pubertal status using the 5-stage criteria described by Tanner
209 (25, 26). Boys were defined as having entered clinical puberty if their testicular volume assessed by
210 an orchidometer was ≥ 4 ml (Tanner Stage ≥ 2). Girls were defined as having entered clinical puberty
211 if their breast development had started (Tanner Stage ≥ 2). Among TDCOB controls, pubertal staging
212 was obtained via a questionnaire with picture pattern recognition of the five different Tanner stages

213 accompanied by a text describing each category. To divide children and adolescents into pre-puberty-
 214 onset and onset/ post-onset groups, children with Tanner Stage 1 were considered pre-onset, and all
 215 others were considered onset/post-onset. Children in the SKOT study (aged 3 years) were all
 216 considered prepubertal. Children 8-11 years of age in the ALSPAC were excluded from analyses
 217 using puberty stratification due to insufficient information on puberty. These assessments have been
 218 previously described in detail for each study population (18, 27-31).

219 *Genotyping, imputation and genetic risk score construction*

220 Children in YFS, TDCOB, and SKOT were genotyped using the Illumina Infinium
 221 HumanCoreExome BeadChip (Illumina, San Diego, CA, USA) (32). Children in STRIP were
 222 genotyped using the Illumina Cardio-MetaboChip (33). Children in PANIC were genotyped using
 223 the Illumina HumanCoreExome Beadchip and the Illumina Cardio-MetaboChip, and the genotypes
 224 from the two arrays were combined. Children in ALSPAC were genotyped using the Illumina
 225 HumanHap550 Quad chip. In all studies, genotype imputation was performed using the 1000
 226 Genomes reference panel (34).

227 To construct the WHR_{adjBMI} GRS, we used 49 single nucleotide polymorphisms (SNPs) known
 228 to associate with WHR_{adjBMI} in the largest available genome-wide association study (GWAS)
 229 published at the time of the present analyses, including up to 224,459 adults from the Genetic
 230 Investigation of Anthropometric Traits (GIANT) consortium (7) (**Supplemental Table 1**). One of
 231 the SNPs, rs7759742, was not available in all six studies of the present meta-analysis and was
 232 therefore excluded from the final GRS. The established WHR_{adjBMI} variants were extracted either as
 233 alleles from the genotyped datasets or dosages from the imputed datasets of each cohort. The GRS
 234 was then calculated as the sum of the number of WHR_{adjBMI} - increasing number of alleles or dosages:
 235 WHR_{adjBMI} genetic risk score = $SNP_1 + SNP_2 + SNP_3 + \dots + SNP_n$; where SNP is the number of alleles
 236 or dosage of the WHR_{adjBMI} -raising allele (i.e. ranging from 0-2 WHR_{adjBMI} -raising alleles per locus).

237 *Statistical methods*

238 All statistical analyses and construction of GRS were performed using R software, version 3.3.1.
239 Linear regression models for inverse normally transformed residuals, adjusted for age, sex, puberty
240 (YFS, TDCOB, STRIP, PANIC), and study group, if needed (SKOT, STRIP), and first three genome-
241 wide principal components were used to examine the associations of WHR_{adjBMI} GRS with
242 cardiometabolic risk factors. For WHR, we additionally adjusted the residuals for BMI. For systolic
243 and diastolic blood pressure, we additionally adjusted the residuals for height. Variables were rank
244 inverse normally transformed to approximate normal distribution with a mean of 0 and a standard
245 deviation (SD) of 1. Thus, the effect sizes are reported in SD units of the inverse normally transformed
246 traits. We also studied the associations of WHR_{adjBMI} GRS with cardiometabolic risk factors stratified
247 by puberty (pre-onset vs. onset/post-onset). The results from the different studies were pooled by
248 fixed effect meta-analyses using the 'meta' package of the R software, version 4.6.0 (35). Independent
249 samples t-test was used to compare differences in the effects of the GRS for cardiometabolic risk
250 factors between groups. The associations of the WHR_{adjBMI} GRS with potential confounding lifestyle
251 factors were examined by linear regression adjusted for age and sex in ALSPAC. We estimated the
252 causal effects of WHR_{adjBMI} on cardiometabolic risk factors using two-staged least-squares regression
253 analyses, implemented in the 'AER' R-package (v1.2-6) including all studies from which information
254 on WHR was available (ALSPAC, TDCOB, STRIP, PANIC). We tested for differences between the
255 estimates from linear regression and instrumental variable analyses using the Durbin-Wu-Hausman
256 test and assessed the strength of the genetic instrument by calculating the F-statistic (36). We tested
257 for potential directional pleiotropy in the genetic instrument using the intercept from Egger regression
258 implemented in the 'MendelianRandomization' R-package (v0.3.0). Hereby, deviation of the Egger
259 intercept from zero provides evidence for pleiotropy (37). Using the same package we performed
260 additional sensitivity analyses to confirm that the direction of effect that we observed in least squares

261 regression analysis was consistent with effect estimates based on multiple genetic variants derived
262 from Egger regression and weighted median methods.

263

264 **Results**

265 *Characteristics*

266 Of the 9,895 children and adolescents, 50% were girls and 22% exhibited overweight or obesity
267 (**Table 1**). The mean age was 10.0 years (range 2.7-18.0 years). Altogether, 54% of the children and
268 adolescents were defined as pre-pubertal after excluding participants of the ALSPAC study due to
269 lack of information on their pubertal status.

270 *Association of the WHR_{adjBMI} GRS with cardiometabolic risk factors in children and adolescents*

271 A key assumption of the Mendelian randomization approach is that genetic variants used as an
272 instrument are associated with the exposure variable. In a meta-analysis of all 9,895 children and
273 adolescents from the six studies, we found that the WHR_{adjBMI} GRS, calculated as the unweighted
274 sum of the number of WHR_{adjBMI} -raising alleles (7), was robustly associated with higher WHR_{adjBMI}
275 ($\beta=0.021$ SD/allele, CI95% 0.016, 0.026, $P=3\times 10^{-15}$).

276 The primary outcome variables of the present analyses were circulating LDL
277 cholesterol, HDL cholesterol and triglycerides, fasting glucose, fasting insulin, systolic blood
278 pressure, and diastolic blood pressure. We found that the WHR_{adjBMI} -increasing GRS was associated
279 with unfavorable concentrations of blood lipids (higher LDL cholesterol: $\beta=0.006$ SD/allele, CI
280 95% 0.001, 0.011, $P=0.025$; lower HDL cholesterol: $\beta=-0.007$ SD/allele, CI95% -0.012, -0.002,
281 $P=0.009$; higher triglycerides: $\beta=0.007$ SD/allele, CI95% 0.002, 0.012, $P=0.006$). There were no
282 associations between the WHR_{adjBMI} GRS and fasting glucose, fasting insulin, systolic blood pressure
283 or diastolic blood pressure ($P>0.05$) (**Figure 1, Supplemental Table 2, Supplemental Figure 2**).

284 In the original GWAS for WHR_{adjBMI} in adults, 20 of the 49 WHR_{adjBMI} loci showed
285 sexual dimorphism, 19 of which displayed a stronger effect in women (7). In sex-stratified analyses,
286 we found that the WHR_{adjBMI} GRS had a comparable effect on WHR_{adjBMI} in boys and girls but the
287 effect on waist circumference was found only in girls (beta=0.013 SD/allele, CI95% 0.005, 0.020,
288 P=0.001) and not in boys (beta=-0.002 SD/allele, CI 95% -0.009, 0.005, P=0.599) (P for
289 difference=0.006). The WHR_{adjBMI} GRS was also associated with decreased BMI-SDS in boys
290 (beta=-0.008 SD/allele, CI95% -0.015, -0.002, P=0.016) but had no effect on BMI-SDS in girls
291 (beta=0.002 SD/allele, CI95% -0.004, 0.009, P=0.450) (P for difference=0.022). Finally, we also
292 found a difference between sexes (P for difference= 3×10^{-4}) in the effect of the WHR_{adjBMI} GRS on
293 diastolic blood pressure; the WHR_{adjBMI} GRS had a blood pressure-increasing effect in girls
294 (beta=0.0109 SD/allele, CI95% 0.005, 0.017, P=0.001) but not in boys (beta=-0.006, 95% CI -0.013,
295 0.001, P=0.072). No differences were found in other cardiometabolic risk factors between girls and
296 boys ($p > 0.05$).

297 A previous mendelian randomization study in adults (5) found a significant inverse
298 association between the WHR_{adjBMI} GRS and BMI and thus performed sensitivity analyses using a
299 WHR_{adjBMI} GRS where all variants associated with BMI ($P < 0.05$) were excluded. We only found a
300 significant inverse association between the WHR_{adjBMI} GRS and BMI in boys, and thus performed
301 boys-specific sensitivity analyses using a GRS constructed of only those 19 WHR_{adjBMI} SNPs that
302 have not been associated with BMI in the largest GWAS thus far published in adults ($P > 0.05$) (38).
303 Comparing the results between the 19 SNP GRS and the full 48 SNP GRS in boys (**Supplemental**
304 **Table 3**), we found very similar effect sizes in the associations of the two scores with cardiometabolic
305 risk traits, except for the expected differences in BMI and related adiposity measures. The results
306 were similar when comparing effect sizes between the 19 SNP GRS and the 48 SNP GRS in all
307 children (**Supplemental Table 4**).

308 Puberty has a major effect on body fat distribution (39). We performed additional analyses
309 stratified by puberty status to test whether the relationship between WHR_{adjBMI} GRS and
310 cardiometabolic risk factors is established before puberty, but no differences were found ($P>0.05$).

311 A previous study in the TDCOB cohort suggested that there may be differences in genetic
312 influences on body fat distribution between children who are overweight/obese and those who are
313 normal-weight (40). We performed analyses stratified by weight status to test whether the effect of
314 the WHR_{adjBMI} GRS on body fat distribution and cardiometabolic risk is modified by
315 overweight/obesity. The WHR_{adjBMI} GRS was associated with fasting insulin in children and
316 adolescents with overweight/obesity (beta=0.016 SD/allele, CI95% 0.001, 0.032, $P=0.037$) but not in
317 those with normal weight (beta=-0.002 SD/allele, CI95% -0.010, 0.006, $P=0.564$) (P for
318 difference=0.034). Furthermore, the WHR_{adjBMI} GRS was also associated with HDL cholesterol in
319 children with overweight and obesity (beta=-0.018 SD/allele, CI95% -0.030, -0.006, $P=0.036$) but
320 not in children with normal body weight (beta=-0.004 SD/allele CI95% -0.010, 0.001, $P=0.121$) (P
321 for difference=0.036). No differences were found in other cardiometabolic risk factors between
322 children with overweight/obesity and those with normal body weight ($p>0.05$).

323 *Instrumental variable analyses*

324 We estimated the causal effects of WHR_{adjBMI} on the three traits that the WHR_{adjBMI} GRS was
325 significantly associated with (triglycerides, HDL cholesterol, and LDL cholesterol) (**Supplemental**
326 **Table 2**) using two-staged least-squares regression analyses. The observational associations of
327 WHR_{adjBMI} with cardiometabolic risk factors are shown in **Supplemental Table 5**. In two-stage least-
328 squares regression analysis, each genetically instrumented one SD increase in WHR_{adjBMI} increased
329 circulating triglycerides by 0.17 mmol/l (0.35 SD per allele, $P=0.040$, **Figure 2, Supplemental**
330 **Figure 3**) indicating a causal relationship. No difference was found between the observational results
331 and genetically instrumented results in the Durbin-Wu Hausman test ($P_{ALSPAC}>0.05$). There was no
332 evidence of pleiotropy in the genetic instrument using the Egger intercept test (Estimate= -0.001,

333 CI95% -0.011, 0.009, $P_{\text{intercept}}$ for triglycerides=0.841). The estimates from Egger regression and
334 weighted median regression were directionally consistent with those derived from the two-stage least
335 squares method. The two-stage least-squares regression analyses did not suggest that a genetically
336 instrumented increase in $\text{WHR}_{\text{adjBMI}}$ has a causal effect on HDL cholesterol (0.24 SD per allele,
337 $P=0.138$) or LDL cholesterol (0.19 SD per allele, $P=0.259$) (**Figure 2**).

338 To conduct a valid Mendelian randomization analysis, the instrumental variable must
339 not be associated with possible confounders that could bias the relationship between the exposure and
340 the outcome, and it must relate to the outcome phenotype only through its association with the
341 exposure and not through pleiotropy (6). Some lifestyle and environmental factors, for example
342 physical activity and dietary habits, have been associated with body fat distribution (4) and
343 cardiometabolic risk, and could therefore confound the association between $\text{WHR}_{\text{adjBMI}}$ and
344 cardiometabolic risk factors. However, we did not find an association between the $\text{WHR}_{\text{adjBMI}}$ GRS
345 and any of the potential confounders we tested in the ALSPAC cohort, including objectively
346 measured physical activity ($p=0.508$) sedentary time ($p=0.580$), family socioeconomic status
347 ($p=0.676$), total energy intake ($p=0.744$), and dietary intakes (E%) of protein ($p=0.661$), total fat
348 ($p=0.193$), saturated fat ($p=0.413$), monounsaturated fat ($p=0.168$), polyunsaturated fat ($p=0.306$),
349 carbohydrates ($p=0.467$), and added sugar ($p=0.201$). We acknowledge that unobserved confounders
350 could still be present that we were not able to control for.

351

352 **Discussion**

353 In the present study, genetic predisposition to higher $\text{WHR}_{\text{adjBMI}}$ was associated with higher
354 triglycerides, lower HDL cholesterol, and higher LDL cholesterol in children and adolescents. The
355 associations of the $\text{WHR}_{\text{adjBMI}}$ GRS with lipids were similar between prepubertal and pubertal/post-
356 pubertal children and adolescents, indicating that this relationship is established already before

357 puberty. Instrumental variable analyses indicated that higher WHR_{adjBMI} may be causally associated
358 with higher triglycerides.

359 Sex and age have major effects on WHR_{adjBMI} (39). Sexual dimorphism in body
360 composition emerges primarily during pubertal development and is driven by the action of sex
361 steroids (41). Women typically have overall higher body fat content, whereas men have a more central
362 body fat distribution. The WHR_{adjBMI} GRS, constructed of the 49 loci, also shows a stronger effect
363 on WHR_{adjBMI} in women than in men (7). In contrast to adults, we observed that the WHR_{adjBMI} GRS
364 had a comparable effect on WHR_{adjBMI} in children regardless of sex. However, the effect on waist
365 circumference was higher in girls than in boys. Previous studies have shown that sexual dimorphism
366 in body fat distribution is distinct already in the first six years of age, characterized by an average
367 smaller waist and larger hip circumference in girls (42). However, unlike in adulthood, the difference
368 in this age is more pronounced for waist circumference than for hip circumference (42), which could
369 partly explain why the genetic influences on waist circumference seem more pronounced in girls than
370 in boys during childhood but not in adulthood.

371 The effects of the WHR_{adjBMI} GRS on fasting insulin and HDL cholesterol were more
372 pronounced among children and adolescents with overweight/obesity than among those with normal
373 body weight, indicating that higher overall adiposity may enhance the harmful effect of genetic
374 predisposition to abdominal adiposity on insulin resistance and dyslipidemia. Although the biological
375 mechanisms for this enhancement are uncertain, we speculate that higher overall adiposity may lead
376 to a suppressed capacity of subcutaneous fat tissue to store additional fat and a higher deposition of
377 fat in visceral and other ectopic storage sites. The metabolically active visceral fat releases a number
378 of inflammatory cytokines as well as a flux of free fatty acids into portal circulation. This may, in
379 turn, impair hepatic metabolism, thereby leading to reduced hepatic insulin clearance, increased
380 production of triglyceride-rich lipoproteins, and increased hepatic glucose production (43, 44). Thus,
381 increased visceral fat has a central role in the development of insulin resistance. Higher overall

382 adiposity also results in greater storage of abdominal subcutaneous fat which has a high lipolytic
383 activity and increases the flux of free fatty acids, contributing to insulin resistance and cardiovascular
384 risk (45). This impact may be particularly relevant in children who have a relatively large volume of
385 abdominal subcutaneous fat compared to visceral fat (12, 13).

386 Previous studies in adults support the role for gradually increasing visceral fat as a
387 determinant of unfavorable changes in plasma lipid concentrations with advancing age (46). Although
388 the effect sizes of the GRS for WHR_{adjBMI} on WHR_{adjBMI} and cardiometabolic risk factors in children
389 and adolescents in the present study were generally weaker than in adults (7), it remains unclear how
390 age plays into the observed causal relationships as partly different variants may associate with
391 WHR_{adjBMI} in different ages.

392 The strength of the present study is the comprehensive data on anthropometry,
393 cardiometabolic risk factors, and genetic variation from several European child cohorts. To our
394 knowledge, this is the first study investigating the causal associations of abdominal adiposity on
395 cardiometabolic risk factors by Mendelian Randomization in children. Limitations of the study are
396 the use of adult GWAS-based variants for WHR_{adjBMI} , which may not all be associated with
397 abdominal adiposity in children. Furthermore, we did not address the possibility of bi-directional
398 relationships between WHR_{adjBMI} and cardiometabolic risk factors in children. Despite the large
399 sample size, our study may have been underpowered to detect a difference for the studied outcome
400 traits. In the present analysis, we did not correct for multiple testing due to many of the outcome traits
401 being correlated, and we acknowledge that adjustment of the significance threshold could reduce the
402 statistical power further. Finally, as our study only included children of European genetic ancestry,
403 the results cannot be generalized to other ethnic groups.

404

405 **Conclusions**

406 Our results suggest that there may be a causal, unfavorable effect of abdominal adiposity on plasma
407 triglycerides in childhood, providing new insights into the relationship between body fat distribution
408 and cardiometabolic risk in young age. The results underscore the importance of early weight
409 management through healthy dietary habits and physically active lifestyle among children with
410 tendency for abdominal fat accumulation.

411

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420 **Conflicts of interest**

421 The authors declare no conflicts of interest.

422 **Authors' contributions**

423 A.V. and T.M.S researched data, A.V. wrote paper. T.O.K. designed research, Other co-authors
424 conducted research and/or provided essential materials. A.V had primary responsibility for the final
425 content. All authors read and approved the final manuscript.

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Table 1. Characteristics of children and adolescents in the studies included in the present meta-analyses.

| | ALSPAC | YFS | TDCOB cases | TDCOB controls | STRIP | PANIC | SKOT |
|--|-------------|--------------|-------------|----------------|--------------|-------------|-------------|
| N (total) | 5474 | 2099 | 705 | 361 | 470 | 460 | 326 |
| Girls (%) | 2754 (50%) | 1139 (54%) | 415 (59%) | 238 (66%) | 227 (48%) | 219 (48%) | 154 (47%) |
| Prepubertal (%)¹ | NA | 1244 (51%) | 314 (45%) | 73 (22%) | 0 (0%) | 448 (97%) | 326 (100%) |
| Overweight/obese² | 1088 (20%) | 161 (8%) | 699 (99%) | 46 (13%) | 54 (12%) | 56 (12%) | 34 (10%) |
| Age (years) | 9.9 (0.32) | 9.8 (4.0) | 11.5 (2.9) | 13.0 (3.1) | 15.0 (0.0) | 7.6 (0.4) | 3.0 (0.1) |
| Body height (cm) | 139.6 (6.3) | 137 (25) | 152 (16) | 157 (16) | 170 (8) | 129 (6) | 96.2 (3.6) |
| Body weight (kg) | 34.7 (7.3) | 35.1 (16.5) | 64.9 (23.9) | 48.4 (15.3) | 61.3 (6.9) | 26.7 (4.8) | 14.9 (1.7) |
| BMI (kg/cm²) | 17.7 (2.8) | 17.4 (2.8) | 27.0 (5.3) | 19.1 (3.2) | 20.5 (3.3) | 16.1 (2.0) | 16.1 (1.2) |
| BMI-SDS | 0.29 (1.11) | -0.29 (1.00) | 2.90 (0.66) | 0.31 (1.05) | -0.08 (0.97) | -0.20 (1.1) | 0.43 (0.92) |
| Waist circumference (cm) | 62.9 (7.7) | NA | 93 (15) | 70 (9) | 73 (8) | 57 (5) | 47 (4) |
| Waist-hip-ratio | 0.85 (0.0) | NA | 0.97 (0.07) | 0.82 (0.1) | 0.80 (0.05) | 0.85 (0.0) | NA |
| Total body lean mass (kg) | 24.6 (3.2) | NA | NA | NA | 45 (9) | 21 (2) | NA |
| Total body fat mass (kg) | 8.5 (5.0) | NA | 28.0 (12.2) | NA | 12.7 (7.5) | 5.6 (3.3) | 2.6 (0.8) |
| Body fat percentage (%) | 23.2 (9.0) | NA | 43.6 (5.2) | NA | 20.9 (9.3) | 20 (8) | 17.4 (4.3) |
| Insulin (mU/l) | NA | 9.2 (5.8) | 6.9 (7.2) | 4.5 (2.2) | 8.3 (3.5) | 4.5 (2.5) | 3.2 (3.5) |
| Glucose (mmol/l) | NA | NA | 5.2 (0.6) | 5.4 (1.1) | 4.9 (0.3) | 4.8 (0.4) | 4.8 (0.6) |
| LDL cholesterol (mmol/l) | 2.3 (0.6) | 3.5 (0.8) | 2.5 (0.8) | 2.2 (0.5) | 2.4 (0.7) | 2.3 (0.5) | 2.5 (0.6) |
| HDL cholesterol (mmol/l) | 1.4 (0.3) | 1.6 (0.3) | 1.2 (0.3) | 1.5 (0.3) | 1.2 (0.2) | 1.6 (0.3) | 1.2 (0.2) |
| Triglycerides (mmol/l) | 1.1 (0.6) | 0.65 (0.29) | 1.1 (0.6) | 0.7 (0.3) | 0.85 (0.42) | 0.60 (0.25) | 1.1 (0.6) |
| Systolic blood pressure (mmHg) | 103 (9) | 111 (12) | 114 (12) | 114 (10) | 117 /12) | 100 (7) | 96 (8) |
| Diastolic blood pressure (mmHg) | 57 (6) | 68 (9) | 65 (8) | 62 (7) | 61 (9) | 61 (7) | 61 (7) |
| GRS_{WHRadjBMI}, 48 SNPs (number of WHR_{adjBMI} increasing risk alleles) | 46.1 (4.3) | 47.8 (4.4) | 46.4 (4.3) | 46.2 (4.3) | 46.6 (4.8) | 48.2 (4.2) | 46.5 (4.4) |

Values are mean (SD) or *n* (%). BMI-SDS= body mass index standard deviation score; GRS= genetic risk score, WHR_{adjBMI}= waist hip ratio adjusted BMI

¹ Children with Tanner Stage 1 were considered pre-onset and all others were considered onset/post-onset (25, 26).

² Overweight and obesity were defined using the age and sex-specific BMI cut-offs of the International Obesity Task Force (IOTF) (24).

Figure 1.

Linear regression analysis to test the association of the WHR_{adjBMI} -increasing genetic score with cardiometabolic variables in all children and adolescents ($n=9,895$). The results are expressed as beta values (confidence intervals) of the inverse-normally transformed traits and are aligned according to the WHR_{adjBMI} -increasing allele of the genetic score. All analyses are adjusted for age, puberty, and first three genome-wide principal components. The effects were pooled using fixed effects models meta-analyses. *P-values <0.05 . [beta in SD/allele = effect on the inverse-normally transformed trait per allele increase]. The numerical values for betas, standard errors, P-values, and sample sizes are presented in **Supplemental Table 2**.

Figure 2. Mendelian randomization analysis to test the causal effect of childhood abdominal adiposity on LDL cholesterol, HDL cholesterol and triglycerides. The figure shows associations of the WHR_{adjBMI} genetic risk score with LDL cholesterol, HDL cholesterol, triglycerides and observational WHR_{adjBMI} , as well as the associations of the observational WHR_{adjBMI} with LDL cholesterol, HDL cholesterol and triglycerides. The results of instrumental analysis are obtained from two-staged least-squares regression analyses. Beta values are expressed as units of standard deviation (SD) of the inverse-normally transformed traits. [beta in SD/allele = effect on the inverse-normally transformed trait per allele increase]. P-values <0.05 are shown in bold.